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Potential contribution of mesenchymal stem/stromal cell senescence into the pathogenesis of age-associated vascular diseases

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Background. Mesenchymal stem/stromal cells (MSC) being an important component of niches of almost all types of resident stem cells were shown to regulate the balance between tissue repair and regeneration. Due to the perivascular location MSC can respond to a wide range of regulatory signals and reprogram the microenvironment by producing various mediators, including regulatory non-coding RNAs secreted within extracellular vesicles (EV). Therefore, modulating the regulatory properties of these cells under the influence of signals from damaged tissues throughout the life, which do not cause cell death, but lead to significant changes in their functional activity, is extremely urgent. The purpose of our study was to evaluate the properties of MSC from aged patients that could contribute into the pathogenesis of age-associated vascular diseases.

Methods. MSC were isolated from subcutaneous fat tissue samples of 57 aged patients (age > 65 years) and 10 control patients (age < 40 years) during surgical operations. Cells were characterized as MSC according to their immunophenotype and differentiation capacity. Markers of senescent cell accumulation and MSC secretion profile were evaluated by different established techniques.

Results. We showed that MSC derived from aged patients acquire signs of senescent cells characterized by cell cycle arrest, induction of p16 and p21 expression, telomere shortening (with 3-fold decrease of absolute telomere length in aged patients) and decreased telomerase activity, enhanced b-galactosidase expression, impaired efficiency of the DNA repair system (higher number of pH2AX-positive cells) and specific age-associated secretion profile (SASP). These cells secreted higher amount of interleukin-6, monocyte chemoattractant protein-1 (MCP-1), urokinase, plasminogen activator inhibitor-1 (PAI-1) and osteonectin and less proangiogenic factors such as vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF). Increasing age inversely correlated with summary tube length formed by endothelial cells in the presence of MSC conditioned media ($r = -0{,}53$, $p=0{,}03$) in tube assay. We also revealed a specific shift of the pattern of microRNA contained in EV produced by MSC from aged patients with activation of pro-senescent and pro-fibrotic gene expression pattern in target cells.

Conclusions. We have shown that under the influence of the processes occurring in the human body during aging, accelerated aging of MSC and accumulation of cells with the properties of senescent among them occur. It could have a significant effect on their microenvironment during adaptive remodeling of damaged tissues, largely due to changes in their secretion. Given the critical role of MSC in the regulation of tissue healing after damage, long-term preservation of such senescent cells in the tissues can lead to a deterioration in the regenerative functions of tissues and can cause the pathogenesis of many age-associated diseases.